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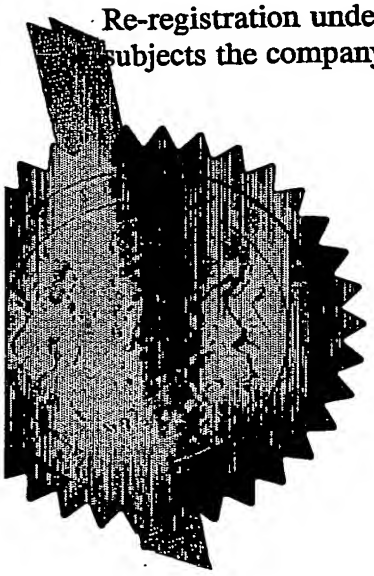

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1.	Your reference	G-33434/P1/9945
2.	Patent application number *(The Patent Office will fill in this part)*	0325174.1 — 28 OCT 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	SANDOZ GMBH BIOCHEMIESTRASSE 10 A-6250 KUNDL, TIROL AUSTRIA
	Patent ADP number *(if you know it)*	8638736001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Bernard A. Marsh
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country — Priority application number *(if you know it)* — Date of filing (day/month/year)
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Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application

Signature Date

Bernard A. Marsh 28th October 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew 01403 323069

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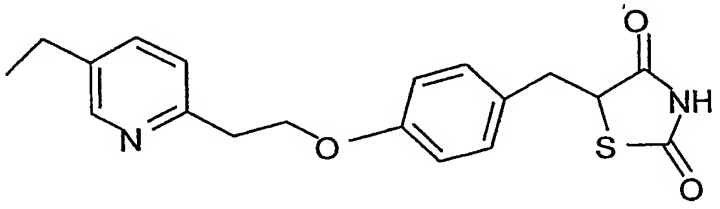
Organic Compounds

The present invention relates to a new process for preparing thiazolidinedione compounds that includes the step of reduction of a thiazolidinedione precursor. More particularly, the present invention relates to thiazolidinedione compounds having antihyperglycemic properties.

Thiazolidinedione antihyperglycemic compounds are a class of pharmaceuticals acting by primarily decreasing insulin resistance in patients suffering from non-insulin-dependent diabetes. Therefore thiazolidinedione antihyperglycemic compounds are used typically as active substances in various pharmaceutical preparations for the treatment of type II diabetes and other disorders related to insulin resistance.

Pioglitazone (5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, according to Merck Index/13th Edition/Monograph number 7533, CAS Registry number: 111025-46-8) has the formula I



I

and is used as active substance in pharmaceutical preparations which are used as oral antihyperglycemic agents.
Pioglitazone is currently marketed as pioglitazone hydrochloride (5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride).

Rosiglitazone (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, according to Merck Index/13th Edition/Monograph number 8346, CAS Registry number: 122320-73-4), and troglitazone (5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione, according to Merck Index/13th Edition/Monograph number 9838, CAS Registry number: 97322-87-7) are other thiazolidinedione antihyperglycemic compounds useful for treating type II diabetes and other disorders related to insulin resistance.

Processes for making pioglitazone, rosiglitazone and troglitazone may proceed via a thiazolidinedione precursor having an exocyclic carbon-carbon double bond at the 5-position of the thiazolidinedione moiety. In such methods, the carbon-carbon double bond is e.g. hydrogenated to a carbon-carbon single bond to form the thiazolidinedione antihyperglycemic compound; inter alia, catalytic hydrogenation over a supported catalyst may be applied as known.

A method for making pioglitazone, for example, is disclosed in US patent US 5952509. Most known processes comprise demanding methods involving e.g. the above mentioned catalysts, or e.g. the use of cobalt ions. These methods apply agents which are either relatively expensive and/or ecologically critical regarding their handling, and which are often combined with the use of hydrogen the handling of which requires costly safety measures and special reaction apparatus.

Surprisingly, the present inventors have found that reduction of the thiazolidinedione precursor to form the corresponding thiazolidinedione antihyperglycemic compound may be effected in a simple and cost-effective way, which makes it more attractive from an industrial and ecological point of view.

In one aspect therefore, the present invention provides a process for reducing an exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor comprising the steps of:

a) preparing a solution or suspension of the thiazolidinedione precursor in a solvent medium with a base, and

b) combining the solution or suspension with a dithionite source.

The dithionite source may comprise sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkylammonium- or a guanidinium-dithionite.
Without wishing to be bound by any particular mechanism or theory, the present applicants believe that the dithionite source acts as a reducing agent.

The solution or suspension of the thiazolidinedione precursor in the solvent medium with the base may be combined with the dithionite source at elevated temperatures.

In another aspect, the process of the present invention may further comprise isolation of the reduced thiazolidinedione precursor.

In another aspect, the present invention provides a process for preparing a thiazolidinedione antihyperglycemic compound comprising reduction of the exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor, especially a thiazolidinedione precursor of pioglitazone, rosiglitazone, or troglitazone, which process comprises the steps of:

a) preparing a solution or suspension of the thiazolidinedione precursor in a solvent medium with a base, and heating the solution or suspension to a temperature of about 40°C to 100°C,

b) combining the solution or suspension with a dithionite source selected from the group of sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkylammonium- or a guanidinium-dithionite, to provide a reaction mixture,

c) maintaining the reaction mixture at a temperature of about 40°C to 100°C for about 1 to 10 hours, and

d) isolating the resulting thiazolidinedione antihyperglycemic compound as free base.

The reaction mixture may be cooled to about 0°C to 30°C before isolation of the thiazolidinedione antihyperglycemic compound.

The present invention provides therefore a process for preparing pioglitazone including the step of reducing the pioglitazone precursor 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione comprising the above mentioned steps and isolating pioglitazone free base.

In a further aspect, the present invention provides a process for preparing rosiglitazone including the step of reducing the rosiglitazone precursor 5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methenyl-2,4-thiazolidinedione comprising the above mentioned steps and isolating rosiglitazone free base.

In still a further aspect, the present invention provides a process for preparing troglitazone including the step of reducing the troglitazone precursor 5-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methenyl-2,4-thiazolidinedione comprising the above mentioned steps and isolating troglitazone free base.

In another aspect of the invention, the selective reduction process as herein described may take place in the presence of a phase-transfer catalyst.

Depending on the thiazolidinedione precursor selected, the process as described herein may lead to the corresponding thiazolidinedione antihyperglycemic compound in the form of the free base, which is obtained, e.g. in crystalline form, in a high yield and with high purity.

The free base of the thiazolidinedione antihyperglycemic compound may be further purified and/or converted to a derivative, e.g. to a pharmaceutically acceptable salt, e.g. to the hydrochloride in case of pioglitazone, or e.g. to the maleate in case of rosiglitazone, by known methods.

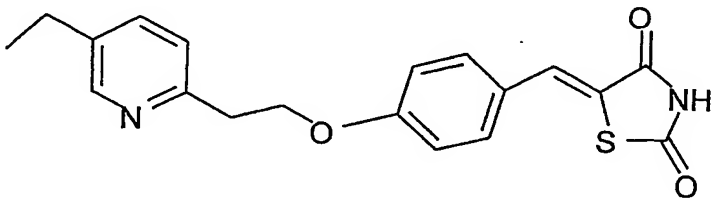
A "thiazolidinedione precursor" as used herein, is understood to mean a compound which is an intermediate in a process for making a thiazolidinedione antihyperglycemic compound, such as the process disclosed in US patent 5952509 incorporated herein by reference, and that has a thiazolidinedione moiety.

A preferred thiazolidinedione precursor is a precursor which differs structurally from the corresponding thiazolidinedione antihyperglycemic compound itself in that the preferred thiazolidinedione precursor has an exocyclic double bond at the 5-position of the thiazolidinedione moiety.

A preferred thiazolidinedione precursor may have protected functional groups e.g. protected hydroxyl groups.

The selective reduction of the above mentioned exocyclic double bond, and removal of protecting groups if any, yields the thiazolidinedione antihyperglycemic compound which may subsequently be isolated from the reaction mixture.

The compound 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione, having the formula II



II

is an example of a preferred thiazolidinedione precursor for pioglitazone, which may be prepared according to the method of Saito et al. disclosed in US patent 5952509, or in published European patent application EP 0816340.

The compound 5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methenyl-2,4-thiazolidinedione is an example of a preferred thiazolidinedione precursor for rosiglitazone, and is disclosed, for example, in US patent 5002953.

The compound 5-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methenyl-2,4-thiazolidinedione, or hydroxy group protected derivatives thereof, are examples of preferred thiazolidinedione precursors for troglitazone, as disclosed e.g. in J. Crossy et al., Bioorganic and Medicinal Chemistry Letters 9, pp. 3439, 1999.

In one embodiment, the process according to the present invention is carried out as follows:

A solution or suspension is prepared by combining a thiazolidinedione precursor, e.g. a preferred thiazolidinedione precursor of pioglitazone, e.g. 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione, with 5 to 100 volumes of a suitable solvent medium, and with 1 to 30 molar equivalents, preferably 5 to 15 molar equivalents, of a suitable base. Molar equivalents mean "as compared to the thiazolidinedione precursor used".

Suitable bases comprise an alkaline or alkaline earth carbonate, e.g. sodium carbonate, potassium carbonate or lithium carbonate, an alkaline hydrogen carbonate, e.g. sodium bicarbonate, an organic secondary or tertiary amine, e.g. piperidine, or an amidine, e.g. DBU (i.e. 1,8-diazabicyclo[5.4.0]undec-7-en).
Preferred bases comprise sodium carbonate or potassium carbonate.

A suitable solvent medium may comprise an aqueous medium, which includes water or a mixture of water with one or more organic solvents, wherein the ratio of water to organic solvent/s may be 10 : 1 to 1 : 10 (v/v).
Suitable organic solvents include alcohols, for example methanol, ethanol or isopropanol, alkyl esters such as ethyl acetate, aromatic hydrocarbons, e.g. toluene or xylene, halogenated hydrocarbons, e.g. methylene chloride, ethers such as tetrahydrofuran or dioxane, and amides, e.g. N,N-dimethylformamide.
A preferred solvent mixture is N,N-dimethylformamide and water.

The resulting mixture of the thiazolidinedione precursor, the base and the solvent medium, is subsequently heated to an elevated temperature of about 40° to 100°C, preferably of about 50°C to 90°C , most preferably of about 60°C to 80°C.

At the elevated temperature as mentioned above, 1 to 30 molar equivalents, preferably 5 to 20 molar equivalents (as compared to the thiazolidinedione precursor used), of the dithionite source may be added either in portions or, e.g. drop-wise, as a solution, preferably in water, over a period of a few minutes up to 2 hours, preferably over a period of about 30 min to 1 hour. The resulting reaction mixture is subsequently maintained at the above mentioned elevated temperature during the reduction process, which lasts for about 1 to 10 hours depending on the temperature employed, e.g. for about 1 to 3 hours if the temperature is maintained at about 80°C.

Suitable dithionite sources comprise sodium-, lithium-, potassium-, calcium-, magnesium-, aluminium-dithionite, or a tetraalkylammonium-dithionite, e.g. a tetraethylammonium-dithionite, or a guanidinium-dithionite.
A preferred dithionite source is sodium dithionite.

After the completion of the reduction process as herein described, the reduced thiazolidinedione precursor may be isolated from the reaction mixture.

Depending on the solvent or solvent mixture used, the reaction mixture may be cooled to induce or enhance crystallization. The cooling procedure may be effected stepwise, e.g. in a first step to a temperature of about 50°C, and subsequently to about 30°C to 0°C , preferably to about 10 °C.
Alternatively, the cooling procedure may be performed so as to provide a substantially constant rate of temperature decrease.

If necessary, and depending on the solvent medium and base used, the pH-value may be adjusted to about 2 to 8, preferably to about 5 to 6, most preferably to about 6, by adding, e.g. acetic acid, e.g. 50 to 60% (v/v) aqueous acetic acid.

The precipitate formed may subsequently be collected by conventional methods such as filtration, washing and vacuum drying.

The resulting free base of the thiazolidinedione antihyperglycemic compound, e.g. pioglitazone free base, may be obtained, e.g. in crystalline form, with good to excellent yields, e.g. of about 70 to 90% (as related to the corresponding thiazolidinedione precursor), and having a high purity, e.g. as defined by a HPLC-purity of about 80% to 98% with respect to impurities and depending on the solvent or solvent mixture used.

If the reduction process takes place in the preferred solvent mixture, i.e. N,N-dimethylformamide and water, purity may typically exceed 95 %, and the resulting pioglitazone free base may be converted directly to pioglitazone hydrochloride.

In another embodiment, the reduction process as described above may be carried out in the presence of a phase-transfer catalyst. A suitable phase-transfer catalyst may comprise e.g. a tetrabutylammonium halide, a tetraethylammonium halide or a benzyl tributylammonium halide. "Halide" as used herein is understood to mean a bromide, chloride or fluoride of the corresponding compound.

The reduction process as described for the present invention is highly selective, which means that side-products may be formed in small amounts only and which may typically be removed during the subsequent processing of the base of the thiazolidinedione antihyperglycemic compound to a purified form of said base and/or to a derivative thereof, e.g. in the case of pioglitazone, a hydrochloride form.

The free base of the thiazolidinedione antihyperglycemic compound may be further purified by known methods, e.g. by tituration with alcoholic solvents, or by standard crystallization procedures, e.g. using organic solvents, e.g. dioxane or N,N-dimethylformamide, as crystallisation solvents.

In a further aspect of the invention, pioglitazone free base as obtained by the process herein described, may be processed to the hydrochloride form by known methods, optionally after a purification step as described above.

In a preferred embodiment, pioglitazone free base as obtained by the reduction process of the invention, is converted to the hydrochloride form by dissolving the crystals of the free base in a solvent, e.g. in an alcohol, e.g. ethanol, e.g. in 1 to 10 volumes, preferably 1 to 6 volumes, of ethanol, and

a) by adding hydrochloric acid, e.g. aqueous hydrochloric acid, e.g. 1 to10 volumes, preferably 1 to 6 volumes, of 2 N HCl, or
b) by adding an ethanol containing hydrochloric acid, e.g. ethanolic hydrochloric acid, e.g. 1 to 10 volumes, preferably 1 to 6 volumes, of about 20% (w/v) ethanolic hydrochloric acid,

at temperatures of e.g. about 40°C to 70 °C, and by subsequently crystallizing the hydrochloride salt from the resulting solution by gradual cooling in order to obtain pure pioglitazone HCl, e.g. with a HPLC-purity of > 98%.

Further purification of the pioglitazone HCl obtained as described above may be performed by known methods, e.g. by recrystallization from a solvent selected from the group of N,N-dimethylformamide, dimethyl acetamide, acetic acid, methanol, ethylene glycol, isopropyl alcohol and t-butyl alcohol.

In addition, pioglitazone HCl may be recrystallized from ethanol as disclosed by Sodha et al., Arzneim.-Forschung/Drug Res. 40 (I), No. 1, 1990, pp. 37.

Pioglitazone HCl obtained by the above described conversion of the pioglitazone free base as obtained by the present invention, corresponds to the known anhydrous crystalline form I.

Form I pioglitazone HCl may be used for the conversion to known crystalline pioglitazone form II employing known methods.

The free base of the thiazolidinedione antihyperglycemic compounds obtained according to the invention, and the derivatives thereof, e.g. pioglitazone HCl, may be used for the manufacture of pharmaceutical compositions which are useful for the treatment of patients suffering from diabetes type II or diseases in which insulin resistance is the underlying pathophysiological mechanism.

Following is a description by way of example only of processes according to the invention. All temperatures are given in degree Celsius and are uncorrected.

Example 1 :

Preparation of pioglitazone free base using sodium carbonate as base and a 1 : 1 mixture of dioxane and water as solvent medium

To a solution of 19.5 g sodium carbonate in 75 ml water, 5 g of 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione are added followed by 75 ml dioxane in a round-bottomed flask. The resulting mixture is then heated to about 80°C under agitation. At about 80°C a solution of 28 g of sodium dithionite in 150 ml water is added drop-wise within about 60 minutes. The reaction mixture is stirred at about 80°C for approximately one hour, then cooled to about 50°C and subsequently stirred at about 50°C for about one hour before cooling to about 10°C. The pH-value is adjusted to about 6 with 50 ml of 60% (v/v) aqueous acetic acid, and the reaction mixture is then stirred at about 10°C for

about 30 minutes. The precipitate formed is filtered, washed with 100 ml water, and the title compound is collected after drying in a vacuum oven for about 8 hours at approximately 65°C.
Yield (crystalline pioglitazone free base): 4.1 g (82% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 97.2%.

Example 2 :
Preparation of pioglitazone free base using potassium carbonate as base and a 1 : 2 mixture of dioxane and water as solvent medium

The conditions and procedure are followed as for Example 1, but using 15.6 g potassium carbonate instead of 19.5 g of sodium carbonate, and 150 ml dioxane instead of 75 ml, and 14.7 g of sodium dithionite in 75 ml water instead of 28 g of sodium dithionite in 150 ml water.
Yield (crystalline pioglitazone free base): 4.1 g (82% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 97.2%.

Example 3 :
Preparation of pioglitazone free base using potassium carbonate as base and a mixture of ethyl acetate and water as solvent medium

The conditions and procedure of Example 2 are followed, but using a 1 : 2 mixture of ethyl acetate and water, i.e. a mixture of 75 ml ethyl acetate and 150 ml water, instead of a mixture of dioxane and water, as solvent medium.
Yield (crystalline pioglitazone free base): 3.5 g (70% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 90%.

Example 4 :
Preparation of pioglitazone free base using potassium carbonate as base and a mixture of N,N-dimethylformamide and water as solvent medium

The conditions and procedure of Example 2 are followed, but using a 1: 6 mixture of N,N-dimethylformamide and water, i.e. a mixture of 25 ml of N,N-dimethylformamide and 150 ml water, instead of a mixture of dioxane and water, as solvent medium.

Yield (crystalline pioglitazone free base): 3.6 g (72% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 98%.

Example 5 :

Preparation of pioglitazone free base using potassium carbonate as base and water as solvent medium

The conditions and procedure of Example 2 are followed, but using 225 ml water instead of a mixture of dioxane and water, as solvent medium.
Yield (crystalline pioglitazone free base): 3.7 g (74% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 89%.

Example 6 :

Preparation of pioglitazone free base using sodium carbonate as base, a mixture of toluene and water as solvent medium and tetrabutyl ammonium bromide as phase-transfer catalyst

The conditions and procedure are followed as for Example 1, but using a 1 : 3 mixture of toluene and water, i.e. a mixture of 75 ml toluene and 225 ml water, instead of a mixture of dioxane and water, as solvent medium, and adding 0.5 g tetrabutyl ammonium bromide into the round-bottomed flask before heating the resulting mixture.
Yield (crystalline pioglitazone free base): 4.9 g (98% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)
HPLC-purity: 80%.

Example 7 :

Preparation of pioglitazone free base using potassium carbonate as base, a mixture of ethyl acetate and water as solvent medium, and tetrabutylammonium bromide as phase-transfer catalyst

The conditions and procedure of Example 6 are followed, but using 15.6 g potassium carbonate instead of sodium carbonate, and a 1 : 2 mixture of ethyl acetate and water, i.e. a mixture of 75 ml ethyl acetate and 150 ml water, instead of a mixture of toluene and water as solvent medium.
Yield (crystalline pioglitazone free base): 3.5 g (70% w/w related to 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione)

HPLC-purity: 90%.

Example 8:

Preparation of pioglitazone hydrochloride from pioglitazone free base using ethanolic hydrochloric acid

6 g of 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, i.e. crystalline free base of pioglitazone as obtained from Example 1, are added to 24 ml ethanol and 12 ml of ethanolic HCl (20% w/v) into a round-bottomed flask. Under stirring the resulting mixture is heated to about 65°C, and is subsequently stirred for about 15 minutes, then gradually cooled to about 30°C within about 2 hours, again stirred at about 30°C for one hour, and subsequently further cooled to about 10°C and stirred for about 1 hour. The precipitate formed is filtered, washed with 30 ml of ethanol, suck-dried, and the title compound is collected after drying under vacuum at about 65°C for about 10 hours.
Yield (crystalline pioglitazone HCl): 5.7 g (95% w/w related to crystalline pioglitazone free base)
HPLC-purity: 99.5%.

Example 9:

Preparation of pioglitazone hydrochloride from pioglitazone free base using 2 N HCl and ethanol

The conditions and procedure of Example 8 are followed, but using a 1 : 1 mixture of ethanol and 2 N HCl, i.e. a mixture of 18 ml ethanol and 18 ml 2 N HCl, instead of a mixture of ethanol and ethanolic hydrochloric acid.
Yield (crystalline pioglitazone HCl): 5.4 g (90% w/w related to crystalline pioglitazone free base)
HPLC-purity: 99.5%.

Example 10:

Purification of pioglitazone hydrochloride using ethanol

6 g crystalline pioglitazone hydrochloride, as obtained from Example 8, are added to 120 ml ethanol in a round-bottomed flask. Under stirring the resulting mixture is heated to about 80°C, and is subsequently stirred for about 30 minutes, then gradually cooled to about 30°C within about 2 hours, again stirred at about 30°C for about one hour, and then further cooled to about 10°C and stirred for approximately 1 hour. The precipitate formed is filtered, washed

with 30 ml of ethanol, suck-dried, and the title compound is collected after drying under vacuum at about 65°C for about 10 hours.
Yield (purified crystalline pioglitazone HCl): 5.4 g (90% w/w related to crystalline pioglitazone hydrochloride)
HPLC-purity: 99.9%.

The preparation of thiazolidinedione antihyperglycemic compounds, e.g. pioglitazone, rosiglitazone, or troglitazone, e.g. in the form of their free bases, by reducing selectively their respective preferred thiazolidinedione precursors by using a dithionite source as described in the present invention, involves a novel reduction process which is attractive both from economic and ecological standpoints.

The reduction process of the invention displays the same selectivity related to the reduction of the thiazolidinedione precursors, and leads to the same high yields and high purity of the thiazolidinedione antihyperglycemic compounds, e.g. of the pioglitazone free base and HCl, as hitherto known processes. The process of the present invention offers, however, the advantages of using reaction agents which are readily commercially available, cheap, ecologically "unrisky" and which avoid potentially dangerous handling.

Claims:

1. A process for reducing an exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor comprising the steps of:
   a) preparing a solution or suspension of the thiazolidinedione precursor in a solvent medium with a base, and
   b) combining the solution or suspension with a dithionite source.

2. A process as claimed in claim 1, wherein the solvent medium comprises an aqueous medium which comprises water or a mixture of water with one or more organic solvents.

3. A process as claimed in claim 2, wherein the organic solvent comprises an alcohol, an alkyl ester, an aromatic hydrocarbon, a halogenated hydrocarbon, an ether or an amide, or a mixture thereof.

4. A process as claimed in claim 2 or 3, wherein the organic solvent comprises methanol, ethanol, isopropanol, ethyl acetate, toluene, xylene, methylene chloride, tetrahydrofuran, dioxane or N,N-dimethylformamide, or a mixture thereof.

5. A process as claimed in any preceding claim, wherein the dithionite source comprises sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkylammonium- or a guanidinium-dithionite.

6. A process as claimed in any preceding claim, wherein the dithionite source is sodium dithionite.

7. A process as claimed in claim 1, wherein the base comprises an alkaline or alkaline earth carbonate, an alkaline hydrogen carbonate, an organic secondary or tertiary amine or an amidine.

8. A process as claimed in claim 7, wherein the base comprises sodium carbonate or potassium carbonate.

9. A process as claimed in any preceding claim, which process takes place in the presence of a phase-transfer catalyst.

10. A process as claimed in claim 9, wherein the phase-transfer catalyst comprises a tetrabutylammonium halide, a tetraethylammonium halide or a benzyl tributylammonium halide.

11. A process as claimed in any preceding claim, wherein the thiazolidinedione precursor is 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione or 5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methenyl-2,4-thiazolidinedione.

12. A process as claimed in any preceding claim, wherein the thiazolidinedione precursor is 5-[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methenyl-2,4- thiazolidinedione.

13. A process as claimed in any preceding claim, wherein the solution or suspension of the thiazolidinedione precursor in the solvent medium with the base is combined with the dithionite source at elevated temperatures.

14. A process as claimed in any preceding claim, further comprising the step of isolation of the reduced thiazolidinedione precursor.

15. A process for preparing a thiazolidinedione antihyperglycemic compound comprising reduction of the exocyclic double bond at the 5-position of the thiazolidinedione moiety of the corresponding thiazolidinedione precursor which process comprises the steps of:

a) preparing a solution or suspension of the thiazolidinedione precursor in a solvent medium with a base, and heating the solution or suspension to a temperature of about 40°C to 100°C,

b) combining the solution or suspension with a dithionite source selected from the group of sodium-, lithium-, potassium-, calcium-, magnesium-, a tetraalkylammonium- or a guanidinium-dithionite, to provide a reaction mixture,

c) maintaining the reaction mixture at a temperature of about 40°C to 100°C for about 1 to 10 hours, and

d) isolating the resulting thiazolidinedione antihyperglycemic compound as free base.

16. A process as claimed in claim 15, wherein the thiazolidinedione antihyperglycemic compound is pioglitazone, rosiglitazone or troglitazone.

17. A process for preparing pioglitazone, which process comprises the following steps:
    a) preparing a solution or suspension of 5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methenyl-2,4-thiazolidinedione in a solvent medium with a base, and heating the solution or suspension to a temperature of about 60°C to 80°C,
    b) combining the solution or suspension with sodium dithionite to provide a reaction mixture,
    c) maintaining the reaction mixture at a temperature of about 60°C to 80°C for about 1 to 3 hours, and
    d) isolating pioglitazone as free base.

18. A process as claimed in any of claims 15 to 17, wherein the reaction mixture is cooled to about 0°C to 30°C before isolation of the thiazolidinedione antihyperglycemic compound.

19. Use of pioglitazone free base as obtained by a process as claimed in any one of claims 1 to 11 and 13 to 18, for conversion to the hydrochloride form of pioglitazone.

20. Use of the hydrochloride form of pioglitazone according to claim 19 for conversion from a crystalline hydrochloride form I into a crystalline hydrochloride form II.

21. Use of a thiazolidinedione antihyperglycemic compound, as obtained according to a process as claimed in any of claims 1 to 18, for the manufacture of a medicament for the administration to a mammal in need thereof.

22. Use of pioglitazone as free base or as hydrochloride, as obtained by a process claimed in any of claims 1 to 11 and 13 to 18, for the manufacture of a medicament for the administration to a mammal in need thereof.

23. Use of a dithionite source to reduce selectively an exocyclic double bond at the 5-position of a thiazolidinedione moiety of a thiazolidinedione precursor to obtain the corresponding thiazolidinedione compound.